

- Sub C*
1. (Twice amended) A method of producing a modification in a gene of interest contained in a cell, comprising:
- providing:
 - an in vitro culture of target cells [comripising] comprising isolated embryonic cells containing a gene of interest, said embryonic cells selected from [embryonic stem cells,] fertilized egg cells, [and] cells of 2-cell embryos, and mouse embryonic stem cells;*
 - a chemical agent capable of producing at least one modification in said gene of interest in at least one of said embryonic cells and at least one modification in one or more additional genes;*
 - treating said embryonic cells with said agent under conditions such that a mixture of embryonic cells is produced, said mixture of embryonic cells comprising cells having an unmodified gene of interest and cells having a modified gene of interest; and*
 - isolating said cells having a modified gene of interest*

- B²*
3. (Twice amended) The method of Claim 1, further comprising d) placing at least one of said cells having a modified gene of interest into an environment under conditions so as to generate *[an organism] a non-human animal* comprising said modification in said gene of interest.

- Sub C²*
15. (Twice amended) A method of producing an allelic series of modifications in a gene of interest contained in a cell, comprising:
- providing:
 - an in vitro culture of target cells comprising isolated embryonic cells containing a gene of interest, said embryonic cells selected from [embryonic stem cells,] fertilized egg cells, [and] cells of 2-cell embryos, and mouse embryonic stem cells;*
 - a chemical agent capable of producing at least one modification in said gene of interest in at least one of said embryonic cells;*

- sub C2
B3*
- b) ~~treating said embryonic cells with said agent under conditions such that a mixture of embryonic cells is produced, said mixture of embryonic cells comprising cells having an unmodified gene of interest, cells having a first modification in said gene of interest, and cells having a second modification in said gene of interest; and~~
- c) ~~isolating said cells having a first modification in said gene of interest and said cells having a second modification in said gene of interest, thereby producing an allelic series of modifications in said gene of interest in the isolated cells.~~

B4

17. (Twice amended) The method of Claim 15, further comprising d) placing at least one cell selected from the group consisting of said cells having a first modification in said gene of interest and said cells having a second modification in said gene of interest into an environment under conditions so as to generate [an organism] a non-human animal comprising a modification selected from the group consisting of said first modification in said gene of interest and said second modification in said gene of interest.

B5

31. (Once amended) The method of Claim 3, wherein said [organism] non-human animal is chimeric.

B6

34. (Once amended) The method of Claim 17, wherein said [organism] non-human animal is chimeric.

Please add the following new Claims 35 and 36:

*sub C7
B7*

35. (New) A method of producing a modification in a gene of interest contained in a cell, comprising:

a) providing:

i) an *in vitro* culture of target cells comprising isolated embryonic cells containing a gene of interest, said embryonic cells selected from fertilized egg cells, cells of 2-cell embryos, and mouse embryonic stem cells;

- 5w
C3*
- ii) a chemical agent capable of producing at least one modification in said gene of interest in at least one of said embryonic cells and at least one modification in one or more additional genes;
- b) treating said embryonic cells with said agent under conditions such that a mixture of embryonic cells is produced, said mixture of embryonic cells comprising cells having an unmodified gene of interest and cells having a modified gene of interest;
- c) isolating said cells having a modified gene of interest; and
- d) placing at least one of said cells having a modified gene of interest into an environment under conditions so as to generate a non-human animal comprising said modification in said gene of interest.
- B7*

36. (New) A method of producing an allelic series of modifications in a gene of interest contained in a cell, comprising:

- a) providing:
- i) an *in vitro* culture of target cells comprising isolated embryonic cells containing a gene of interest, said embryonic cells selected from fertilized egg cells, cells of 2-cell embryos, and mouse embryonic stem cells;
- ii) a chemical agent capable of producing at least one modification in said gene of interest in at least one of said embryonic cells;
- b) treating said embryonic cells with said agent under conditions such that a mixture of embryonic cells is produced, said mixture of embryonic cells comprising cells having an unmodified gene of interest, cells having a first modification in said gene of interest, and cells having a second modification in said gene of interest;
- c) isolating said cells having a first modification in said gene of interest and said cells having a second modification in said gene of interest, thereby producing an allelic series of modifications in said gene of interest in the isolated cells; and
- d) placing at least one cell selected from the group consisting of said cells having a first modification in said gene of interest and said cells having a second modification in said gene of interest into an environment under conditions so as to generate a non-human animal comprising a modification selected from the group